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L1	solute adj carrier adj family adj 19 near4 (a2 or member adj 2) or slc19a2 or thiamine adj transporter adj 1 or thtr1 or dda1 or aw322295	30	L1

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1. 20050233327. 23 Mar 05. 20 Oct 05. Methods for identifying small molecules that modulate premature translation termination and nonsense mrna decay. Welch, Ellen, et al. 435/6; C12Q001/68.

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L1 and L2	6

Prev Page Next Page Go to Doc#

***603941** GeneTests, Links

SOLUTE CARRIER FAMILY 19 (THIAMINE TRANSPORTER), MEMBER 2; SLC19A2

Alternative titles; symbols

THIAMINE TRANSPORTER PROTEIN 1; THTR1

Gene map locus 1q23.3

TEXT

Thiamine-responsive megaloblastic anemia syndrome (TRMA; 249270), also known as Rogers syndrome, is an early-onset, autosomal recessive disorder defined by the occurrence of megaloblastic anemia, diabetes mellitus, and sensorineural deafness, responding in varying degrees to thiamine treatment. Neufeld et al. (1997) and Raz et al. (1998) narrowed the TRMA locus from a 16- to a 4-cM interval on 1q23.3, and Banikazemi et al. (1999) further refined the locus to a 1.4-cM interval. Studies by Rindi et al. (1994) and by Stagg et al. (1999) had suggested that deficiency in a high-affinity thiamine transporter may cause this disorder.

Labay et al. (1999) identified the SLC19A2 gene by positional cloning. They assembled a P1-derived artificial chromosome (PAC) contig spanning the TRMA candidate region. This clarified the order of genetic markers across the TRMA locus, provided 9 new polymorphic markers, and narrowed the locus to an approximately 400-kb region. Labay et al. (1999) found that the SLC19A2 gene consists of 6 exons spanning approximately 22.5 kb.

Due to its homology with SLC19A1 (600424), a reduced folate carrier protein, Diaz et al. (1999) identified the SLC19A2 gene in the critical region 1q23.2-q23.3 and cloned the entire SLC19A2 coding region by screening a human fetal brain cDNA library. The SLC19A2 gene encodes a protein of 497 amino acids predicted to have 12 transmembrane domains. Northern blot analysis detected a 4-kb transcript in all tissues tested, most abundantly in skeletal and cardiac muscle.

Fleming et al. (1999) used a candidate gene approach to identify putative thiamine transporters in the 1q23.3 critical region and found mutations in the SLC19A2 gene in 2 families with TRMA, 1 Alaskan, studied by Neufeld et al. (1997), and 1 Turkish-Kurdish living in Switzerland. Fleming et al. (1999) demonstrated that the SLC19A2 gene encodes a functional thiamine transporter.

In all affected individuals in 6 TRMA families, Labay et al. (1999) found mutations in the SLC19A2 gene. They suggested that a defect in the thiamine transporter protein encoded by this gene, called THTR1 by them, may underlie the TRMA syndrome. Among 4 Iranian families with TRMA, Diaz et al. (1999) identified 2 frameshift mutations in exon 2, a 1-bp insertion and a 2-bp deletion, of the SLC19A2 gene.

Raz et al. (2000) summarized knowledge on mutations in the SLC19A2 gene in TRMA patients and identified 4 novel mutations.

ANIMAL MODEL

To generate a mouse model of TRMA, Oishi et al. (2002) disrupted the Slc19a2 gene in mice by homologous recombination in embryonic stem cells. Erythrocytes from the null mice lacked the high-affinity component of thiamine transport. On a thiamine-free diet, null mice developed diabetes mellitus with reduced insulin (176730) secretion and an enhanced response to insulin. The diabetes mellitus resolved after 6 weeks of thiamine repletion. Auditory-evoked brainstem response thresholds were markedly elevated in null mice on a thiamine-free diet, but were normal in wildtype mice treated on that diet as well as thiamine-fed-null mice. Bone marrows from thiamine-deficient null mice were abnormal, with a megaloblastosis affecting the erythroid, myeloid, and megakaryocyte lines.

ALLELIC VARIANTS
(selected examples)

.0001 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, ARG162TER]

In a Pakistani family and in a Japanese family, Labay et al. (1999) found that TRMA (249270) was due to a 484C-T transition in exon 2 of the SLC19A2 gene predicted to cause an arg162-to-ter protein change.

.0002 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, 1-BP DEL, 724C]

In 2 Israeli families with TRMA (249270), Labay et al. (1999) found a 1-bp deletion (724C) in exon 2 of the SLC19A2 gene causing a frameshift at codon 242 and creating a stop at codon 259.

.0003 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, GLY172ASP]

In an Italian family, Labay et al. (1999) found a 515G-A transition in exon 2 of the SLC19A2 gene, predicting a gly172-to-asp amino acid change, as the cause of thiamine-responsive megaloblastic anemia (249270).

.0004 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, TRP250TER]

In an Indian family with TRMA (249270), Labay et al. (1999) found a 750G-A transition in exon 2 of the SLC19A2 gene leading to a nonsense mutation, trp250 to ter, in the protein product.

.0005 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, 1-BP DEL, 885T]

In an Alaskan kindred with TRMA (249270) studied by Neufeld et al. (1997), Fleming et al. (1999) found a 1-bp (thymine) deletion at position 885 of the cDNA sequence of the SLC19A2 gene. The proband was homozygous for the deletion resulting in a frameshift and the introduction of a premature stop codon. In the heterozygotes, the reading frame was lost at position 885.

.0006 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, 2-BP DEL, 1147GT]

In a patient with TRMA (249270) from a Swiss-Kurdish kindred, Fleming et al. (1999) found deletion of GT at positions 1147-1148 of the cDNA sequence of the SLC19A2 gene in homozygous state. The reading frame was lost at position 1148 in a heterozygote. The deletion resulted in a frameshift and immediate stop codon.

.0007 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, 1-BP INS, 242A]

In an Iranian family with TRMA (249270), Diaz et al. (1999) found insertion of an adenine between nucleotide 242 and 243 in exon 2 of the SLC19A2 cDNA, introducing a stop codon at codon 52.

.0008 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, 2-BP DEL, 429TT]

In an Iranian family with TRMA (249270), Diaz et al. (1999) identified a 2-bp deletion involving 429T and 430T of the SLC19A2 gene. Three affected members of the family were studied and found to be homozygous. Two sets of parents and 1 unaffected sib were heterozygous for the mutation.

.0009 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, TRP358TER]

In a girl with TRMA (249270), Scharfe et al. (2000) reported a G-to-A transition at nucleotide 1074 in exon 4 of the SLC19A2 gene, resulting in a trp358-to-ter mutation. In addition to TRMA, the girl had short stature, hepatosplenomegaly, retinal degeneration, and a 2-cm lesion in the parietal lobe without any neurologic correlates. Biochemical analyses of muscle and skin biopsies before thiamine supplementation showed a severe deficiency of pyruvate dehydrogenase and complex I of the respiratory chain. These normalized after thiamine supplementation.

.0010 THIAMINE-RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME [SLC19A2, CYS152THR]

In an African-American female with TRMA (249270) associated with thyroid disease and retinitis pigmentosa, Lagarde et al. (2004) identified a homozygous 152C-T transition in exon 1 of the SCL19A2 gene, resulting in a cys152-to-thr (C152T) mutation. The patient presented at 12 months of age with paroxysmal atrial tachycardia and hepatosplenomegaly. One month later, she developed diabetes mellitus requiring intermittent insulin therapy. At 2.5 years of age, profound sensorineural hearing loss was discovered. By 4 years of age, daily insulin therapy was instituted. She developed optic atrophy, retinitis pigmentosa, and visual impairment by 12 years of age with severe restriction of peripheral vision by 16 years. At age 19 years a thiamine-responsive normocytic anemia was discovered. A diagnosis of autoimmune thyroiditis was made at the age of 20 years. With oral thiamine therapy, her insulin requirement decreased.

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